REMARKS

Claims 15 and 31 – 35 are pending. No amendment is made at this time.

Claims 15 and 31-35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kimura et al. in view of Postma et al. (both cited by Examiner on 1/31/2008). (Office Action, page 2)

The applicant respectfully addresses the Examiner's specific concerns, namely evidence regarding the airway, lungs and oral administration, as follows:

In the airway

The rejection states on p.2 last full sentence (emphasis added):

> The examiner does not find the argument regarding or the empirical data showing TA-270 having a stronger inhibitory effect on the infiltration of the inflammatory cells than theophylline in the airway.

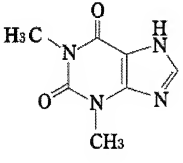
As explained in the December 3, 2009 response p. 5-6 (emphasis added):

> First, in the July 16, 2008 Declaration, the airway inflammation inducing materials (CSS + LPS) were *intratracheally* administered directly into the airway and the test compound was *orally* administered directly into digestive tract. It is hardly believable that all of CSS and LPS intratracheally administered is inactivated by the test compound orally administered.
>
> Second, since the pharmacological effects of the test compound are anti-oxidation and leukotriene biosynthesis inhibition, the test compound can not inactivate CSS and LPS directly. Since the pharmacological effect of theophylline, a commercial drug, is phosphodiesterase inhibition, even theophylline can not inactivate CSS and LPS directly.
>
> The pharmacological evaluation of the Declaration shows that the accumulation or the activation of the inflammatory cells into airway and the following increase of airway tissue obstruction induced by CSS and LPS can be

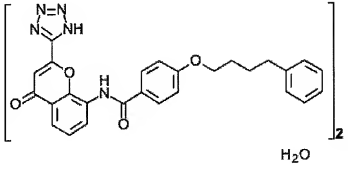
suppressed by the anti-oxidation and leukotriene biosynthesis inhibition of the test compound. Thus, one could evaluate that the test compound suppresses the airway inflammation or deteriorating disease.

Furthermore, the Examiner asserts that Aoki et al. (Eur. J. Pharmacol. (2000); 409:325-330) show at page 328, Table I and page 329, 2nd column, that TA-270 has superior inhibitory effect on the infiltration of inflammatory cells into BAL fluid than Pranlukast, i.e., theophylline. However, as shown below, theophylline is a different compound from Pranlukast. Theophylline has been used for COPD, but Pranlukast has not been used for COPD. There appears to be a misunderstanding regarding the efficacy of Theophylline, as was described in Aoki et al. from before.

Theophylline



Pranlukast



That is to say, Aoki et al. does not show that TA-270 has superior inhibitory effect on the infiltration of inflammatory cells than that of theophylline. In addition, the comparison of the inhibitory effects by TA-270 and theophylline on the infiltration of inflammatory cells at the same dose level was investigated for the first time in the September 28, 2010 Declaration.

As a result, TA-270 showed a more superior inhibitory effect on the infiltration of inflammatory cells into airway by intra-tracheal dose, than theophylline.

Of the Lung

The rejection states on p.3 the first sentence of the first full paragraph (emphasis added):

> It is noted that the 09/28/2010 Declaration provides no empirical data showing the effect of either TA-270 or theophylline on the RV (or FEV1) of the lung.

As explained in the December 3, 2009 response on p. 6 (emphasis added):

> Furthermore, if the test compound inactivates CSS directly, it can be said that the test compound is an useful therapeutic agent considering that cigarette smoke has been known as a main risk factor for COPD and the airway inflammation induced by CSS was suppressed by the test compound.
>
> Accordingly, as demonstrated, it is possible to evaluate the improvement or suppression effect on COPD from the experiment data obtained by administering the test compound to the COPD model induced by CSS and LPS by using the parallel co-administration method. The guinea pig model in the Declaration is COPD model having actual development of the pulmonary emphysema.
>
> As mentioned above, while TA-270 exhibits the same level of improvement with theophylline in the evaluation on "airway resistance," ***TA-270 exhibits an improvement that even theophylline does not exhibit in the evaluation on "residual volume" which is a significant factor in COPD (see Dykstra et al. previously filed).*** TA-270 has in fact an unexpected effect.

Thus the Applicant considers that the significance of TA-270 to theophylline (existing medication) is fully explained by the result of the September 28, 2010 Declaration, as show in part above.

Not orally

The rejection states on p.3 the last sentence of the first full paragraph (emphasis added):

> Even if, *in arguendo*, applicant had provided objective data showing unexpected and superior effects when treating COPD models with TA-270 as compared to an existing medication for COPD, theophylline, the proffered evidence is clearly not commensurate in scope with the claims because the test agents were administered intratracheally – which is not orally and does not support the scope of parenternal administration in the claims.

As explained in the December 3, 2009 response on p. 5-6 (emphasis added):

> First, in the July 16, 2008 Declaration, the airway inflammation inducing materials (CSS + LPS) were *intratracheally* administered directly into the airway and the test compound was *orally* administered directly into digestive tract. It is hardly believable that all of CSS and LPS intratracheally administered is inactivated by the test compound orally administered.
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> Second, since the pharmacological effects of the test compound are anti-oxidation and leukotriene biosynthesis inhibition, the test compound can not inactivate CSS and LPS directly. Since the pharmacological effect of theophylline, a commercial drug, is phosphodiesterase inhibition, even theophylline can not inactivate CSS and LPS directly.
>
> The pharmacological evaluation of the Declaration shows that the accumulation or the activation of the inflammatory cells into airway and the following increase of airway tissue obstruction induced by CSS and LPS can be suppressed by the anti-oxidation and leukotriene biosynthesis inhibition of the test compound. Thus, one could evaluate that the test compound suppresses the airway inflammation or deteriorating disease.

The July 16, 2008 Declaration states on p.4:

To evaluate the effect of compound 551 (100 mg•kg-1) and theophylline (10 mg•kg-1) were orally administered once a day 1 hour before the respective intratracheal instillations of CSS or LPS on days 0-18 (Theophylline group).

The results are shown in FIG. 3.

Note that the administration doses between TA-270 and theophylline were different in Experiment 2 of the July16, 2008 Declaration. Theophylline is moderately toxic after oral uptake and low toxic after dermal and inhalative uptake. LD50, rat (oral): 272 mg/kg bw, LOEAL 37.5 mg/kg bw/d (rat, gavage) (see attached SIDS INITIAL ASSESSMENT PROFILE). Therefore, in Experiment 2, the Applicants used almost a maximum dose of theophylline without side effects such as convulsion, death, and so on, in this repeated dose study. On the other hand, LD50 or NOEAL of TA-270 is more than 2000 mg/kg bw in rats. In experiment 2, a maximum dose (10 mg/kg) of Theophylline with oral administration did not show the efficacy on RV, but 100 mg/kg of TA-270 with oral administration showed significant improvement of RV. Although the Applicants believe that the unexpected effects of TA-270 were shown sufficiently in Experiment 2, the Applicants conducted an additional experiment showing the effects on COPD in the same dose (10 μg/kg) between TA-270 and theophylline in the September 28, 2010 Declaration. In this experiment, TA-270 and theophylline were intra-tracheally administered to avoid systemically toxic effects on COPD mice induced by lipopolysaccharide (LPS). This COPD model was reported in *Am J Physiol Lung Cell Mol Physiol* (295: L1—L15, 2008).

TA-270 showed the significant inhibitory effects on the infiltration of inflammatory cells into airway by intra-tracheal dose at dose of 10 ps/kg. Additionally, TA-270 showed the significant effect by intra-tracheal dose at 24 hour prior to administration of LPS and this long-acting effect meant the possibility that TA-270 was effective in an inhalation dose once a day in COPD patients. These effects were not thought to be related to an allergic reaction through eosinophils because eosinophils could not detect in this COPD model. On the other hand, theophylline did not show any inhibitory effects at a similar dose of TA-270 in any dose timings.

The Declaration dated July 16, 2008 specifically provided experiments and results of *intratracheally* administering, directly into the ***airway***, airway inflammation inducing materials (CSS + LPS) and testing ***orally*** administered compounds on inflamed cells in the airways and

bronchoalveolar cavity (***lungs***), thereby addressing all of the Examiner's specific concerns. Furthermore, as explained in the September 28, 2010 response on p.2:

> However theophylline has a central nervous stimulating effect and a myocardial stimulating effect as side effects and there is not so much of a difference between its efficacious dose and toxic dose…
>
> …The LPS-Induced Model of COPD is known in the art and intra-tracheal administration was chosen to avoid the side-effects of theophylline.

The obvious choice of intra-tracheal administration of theophyline and TA-270 is to avoid the central nervous stimulating effect and a myocardial stimulating effect of theophylline.

The purpose of the Declaration dated September 14, 2010 was to demonstrate further unexpected results of TA-270 on cells in the airway of COPD mice induced by LPS with the original experiments performed in the Declaration dated July 16, 2008. Therefore it is believed that all the empirical data noted by the Examiner in the Office Action has been submitted and is persuasive evidence of unexpected results. Furthermore the data is commensurate in scope with the claims.

It is believed that the invention now claimed is not obvious in light of the combination of cited art. It is respectfully requested that the rejection be reconsidered and withdrawn.

In view of the above remarks, applicant believes the pending application is in condition for allowance.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

Dated: August 24, 2011

Respectfully submitted,

Customer No.: 21874

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Encls: SIDS INITIAL ASSESSMENT PROFILE